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On the Hydrolysis Step in Osmium Catalyzed Asymmetric Dihydroxylations

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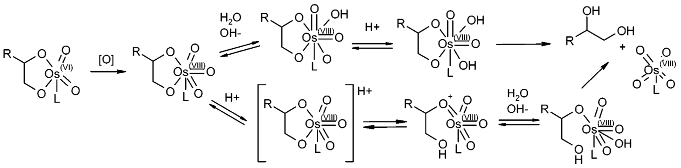

In order to obtain information about the most important features that affect the efficiency of osmium catalyzed asymmetric dihydroxylation, a series of substituted styrenes have been studied by using a Hammett type approach as well as solvent kinetic isotope effects. A concave shaped Hammett plot with a minimum at X = H revealed a change in the mechanism going from electron-donating to electron-withdrawing substituents for both $NaClO_2$ and $K_3[Fe(CN)_6]$ asymmetric dihydroxylations. The Hammett plot together with solvent isotope effect results indicates that osmium (mono)glycolates of styrenes with electron-withdrawing substituents are hydrolyzed by a stepwise attack of the nucleophile to the electrophilic osmium-center and subsequent protonation of the alkaline intermediate. Osmium (mono)glycolates in dihydroxylation, using $NaClO_2$ as the stoichiometric oxidant of styrenes with electron-donating substituents, are hydrolyzed by specific acid catalysis. The rate-limiting step is an A1 type process. Differences in the ρ values in the Hammett plots for $NaClO_2$ and $K_3[Fe(CN)_6]$ asymmetric dihydroxylations indicate that in dihydroxylations with $NaClO_2$ as the secondary oxidant, the reactive osmium(VI) mono(glycolate) is oxidized to osmium(VIII) mono(glycolate) prior to hydrolysis. The reaction rate was found to have an effect on the enantioselectivity in asymmetric dihydroxylation. If the hydrolysis step is slow enough, a competitive bis(glycolation) deteriorates the enantioselectivity in $K_3[Fe(CN)_6]$ asymmetric dihydroxylations and even more so in $NaClO_2$ asymmetric dihydroxylations.

Introduction

Osmium catalyzed dihydroxylation of olefins is one of the most selective and reliable organic transformations. In particular, the catalytic Sharpless asymmetric dihydroxylation in the presence of chiral ligands allows access to a wide variety of enantiomerically pure vicinal diols.[1] Even though a vast amount of research has been made on Sharpless asymmetric dihydroxylation, one can find very little information about the hydrolysis step of the reaction. Knowing the specifics of the process by which the rate-limiting hydrolysis step occurs in this complex reaction would help to develop the efficient and most general asymmetric dihydroxylation method even further. To the best of our knowledge, so far no reports are available on mechanistic studies of the hydrolysis of osmium mono(glycolate) in conditions used in catalytic asymmetric dihydroxylations. We became interested in this subject after we had reported that $NaClO_2$ can be used as the secondary oxidant in Sharpless asymmetric dihydroxylation.[2] The reported $NaClO_2$ dihydroxylations were much faster than the corresponding $K_3[Fe(CN)_6]$ dihydroxylations. In addition, 1,2-disubsituted olefins were dihydroxylated quickly without hydrolysis aids, such as methanesulfonamide. The rate-determining hydrolysis of the osmium mono(glycolate) in asymmetric dihydroxylation was obviously accelerated by changing the secondary $K_3[Fe(CN)_6]$ oxidant to $NaClO_2$. To learn more about the mechanistic details of the rate-limiting hydrolysis step in asymmetric catalytic dihydroxylation, we have performed solvent isotope effect studies together with Hammett type studies of the hydrolysis of osmium mono(glycolate) in catalytic asymmetric $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations. In this paper we report the results from our studies.

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[1] (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, *11*, 1725−1756.

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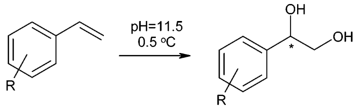
10.1021/jo070011b CCC: $37.00

TABLE 1. Pseudo-First-Order Rate Constants of the Dihydroxylation of 8.5 mM Solutions of Substituted Styrenes in *t*-BuOH/H_2O (1:1)[a]



	NaClO$_2$		K$_3$[Fe(CN)$_6$]		
R	$10^{-4}k$ (s^{-1})	log(k_X/k_H)	$10^{-4}k$ (s^{-1})	log(k_X/k_H)	σ[4]
p-MeO	35.4 ± 0.6[b]	0.76	19.7 ± 0.7	0.50	−0.28
p-Me	14.9 ± 0.3	0.39	11.2 ± 0.3	0.26	−0.14
p-H	6.1 ± 0.1	0.00	6.2 ± 0.1	0.00	0.00
m-Br	8.9 ± 0.2	0.16	7.1 ± 0.4	0.06	0.37
p-CF$_3$	11.4 ± 0.3	0.27	8.0 ± 0.4	0.11	0.53
p-CN	15.0 ± 0.2	0.39	9.6 ± 0.2	0.19	0.70

[a] Reactions were carried out in pseudo-first-order conditions with 85 μmol of olefin, 0.9 mol % of $K_2OsO_4 \cdot 2H_2O$, 2.2 mol % of (DHQD)$_2$PHAL, 6.0 mmol of K_2CO_3, and 0.13 mmol (1.5 equiv) of $NaClO_2$ (80%) or 0.26 mmol (3 equiv) of $K_3[Fe(CN)_6]$ in 10 mL of a *t*-BuOH/H_2O (1:1) mixture. The pH was adjusted to 11.5 with $NaHCO_3$. [b] 95% confidence level.

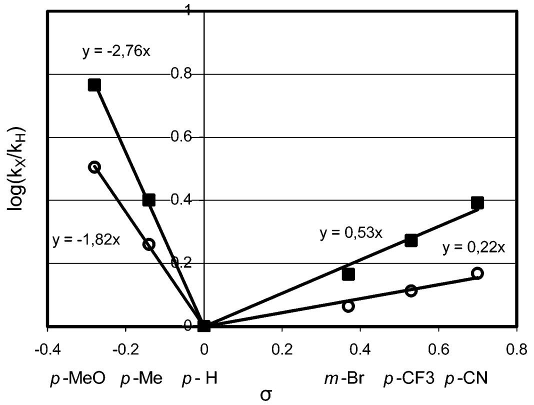


FIGURE 1. Hammett plots for $NaClO_2$ dihydroxylations (■) and $K_3[Fe(CN)_6]$ dihydroxylations (○) under pseudo-first-order reaction conditions.

Results and Discussion

For the Hammett type study, six substituted styrenes were dihydroxylated using pseudo-first-order reaction conditions. Table 1 presents the two sets of pseudo-first-order rate constants that were determined using pH = 11.5 buffered reaction conditions: one for $NaClO_2$ dihydroxylations and one for $K_3[Fe(CN)_6]$ dihydroxylations. k_X and k_H are the pseudo-first-order rate constants of catalytic asymmetric dihydroxylations, and σ is Hammett's σ value. Hammett plots of log(k_X/k_H) vs σ of catalytic asymmetric $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations are presented in Figure 1. The pseudo-first-order rate constants for both oxidants afforded concave shaped Hammett plots with a minimum at X = H. Slopes in the Hammett plot for $NaClO_2$ dihydroxylations are 1.5 and 2.4 times higher than the corresponding slopes in $K_3[Fe(CN)_6]$ dihydroxylations. For electron-donating groups, the ρ value in $NaClO_2$ dihydroxylations was -2.76 ($R^2 = 1$) and for electron-withdrawing groups 0.53 ($R^2 = 0.98$). The corresponding ρ values in $K_3[Fe(CN)_6]$ dihydroxylations were -1.82 ($R^2 = 1$) and 0.22 ($R^2 = 0.97$). The distinct minimum at X = H in the Hammett plots of both $NaClO_2$ dihydroxylations and $K_3[Fe(CN)_6]$ dihydroxylations strongly indicates a change in the mechanism when the substituents on the olefin are changed from electron-donating ones to electron-withdrawing ones.[3]

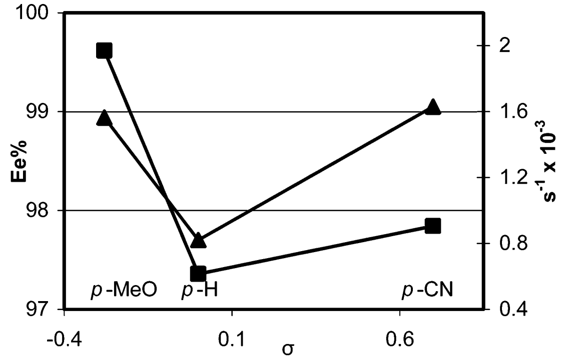


FIGURE 2. Enantioselectivities (▲) and pseudo-first-order rate constants (■) of the $K_3[Fe(CN)_6]$ dihydroxylations of *p*-methoxystyrene, styrene, and *p*-cyanostyrene as a function of the Hammett σ.

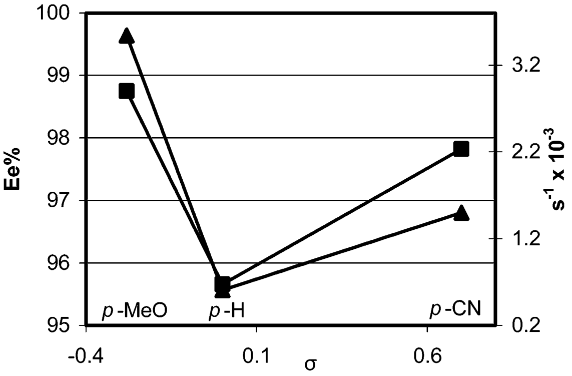


FIGURE 3. Enantioselectivities (■) and pseudo-first-order rate constants (▲) of the $NaClO_2$ dihydroxylations of *p*-methoxystyrene, styrene, and *p*-cyanostyrene as a function of the Hammett σ.

For the kinetic solvent isotope effect studies, *p*-methoxystyrene and *p*-cyanostyrene were dihydroxylated in *t*-BuOH/H_2O (1:1) and in *t*-BuOH/D_2O (1:1) mixtures using both $NaClO_2$ and $K_3[Fe(CN)_6]$ as the secondary oxidants.[5] Pseudo-first-order rate constants from those reactions are presented in Table 2. Rate acceleration was observed when the solvent was changed from H_2O to D_2O in the $NaClO_2$ dihydroxylation of *p*-methoxystyrene. In the corresponding $K_3[Fe(CN)_6]$ dihydroxylation, change was even more dramatic, but for reasons we do not know yet, the pseudo-first-order fitting of ln([a_0]/[a_t]) vs time did not afford a straight line but a curved one when D_2O was the solvent used.[6] In both $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations of electron-withdrawing *p*-cyanostyrene, no significant solvent kinetic isotope effect could be observed.

Sharpless asymmetric dihydroxylation is a three step reaction where different steps take place in different phases in the biphasic reaction mixture: ligand accelerated osmylation of the olefin in the organic phase, hydrolysis of the intermediate glycolate in the border between the water and organic phase,

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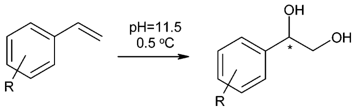
[3] Isaacs, N. S. *Physical Organic Chemistry*; Harlow Longman Scientific & Technical: Essex, U.K., 1987; p 144.

[4] March, J. *Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; p 280.

[5] The H/D exchange is negligible in our solvent system. Balzarek, C.; Weakley, T. J. R.; Tyler, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 9427−9434.

[6] With the variables, a_0 = initial concentration of olefin and a_t = concentration of olefin at a given time.

TABLE 2. Pseudo-First-Order Rate Constants k_{obs} ($\times10^{-4}$ s^{-1}) and Kinetic Solvent Isotope Effects for the Dihydroxylations of *p*-Methoxystyrene and *p*-Cyanostyrene[a]



R	NaClO$_2$			K$_3$[Fe(CN)$_6$]		
	H$_2$O	D$_2$O	k_H/k_D	H$_2$O	D$_2$O	k_H/k_D
p-MeO	35.4 ± 0.6[b]	47.7 ± 1.7	0.74 ± 0.04	19.7 ± 0.7	*c*	
p-CN	15.0 ± 0.2	15.8 ± 0.4	0.95 ± 0.04	9.6 ± 0.2	9.9 ± 0.4	0.97 ± 0.06

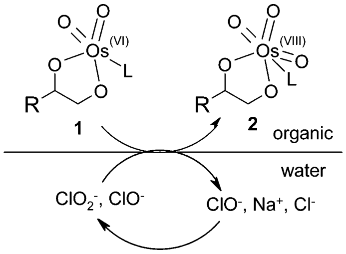
[a] Reactions were carried out in pseudo-first-order conditions with 85 μmol of olefin, 0.9 mol % of $K_2OsO_4 \cdot 2H_2O$, 2.2 mol % of (DHQD)$_2$PHAL, 6.0 mmol of K_2CO_3, and 0.13 mmol (1.5 equiv) of NaClO$_2$ (80%) or 0.26 mmol (3 equiv) of K$_3$[Fe(CN)$_6$] in 10 mL of a *t*-BuOH/H$_2$O or 10 mL of a *t*-BuOH/D$_2$O (1:1) mixture. The pH was adjusted to 11.5 with NaHCO$_3$. [b] 95% confidence level. [c] Reaction did not follow pseudo-first-order kinetics.

and oxidation of the catalyst in the water layer.[7] Results from our reaction rate measurements indicate clearly that the rate-determining step in Sharpless asymmetric dihydroxylation is the hydrolysis of the intermediate glycolate (Table 1). If the oxidation of the catalyst, which takes place in the water layer, is the rate-determining step, we should have obtained only two reaction rates arising from the different oxidation powers of the two different oxidants, NaClO$_2$ and K$_3$[Fe(CN)$_6$]. In NaClO$_2$ dihydroxylations as well as in K$_3$[Fe(CN)$_6$] dihydroxylations of the six substituted styrenes, we measured different reaction rates for all six styrenes.

If the ligand accelerated osmylation was the rate-determining step, one would not expect any difference in reaction rates obtained in NaClO$_2$ and K$_3$[Fe(CN)$_6$] dihydroxylations. The inorganic oxidant, which is dissolved in water, is apart from the organic phase where the osmylation step occurs. The only difference in reaction rates would then emerge from the electronic effects of the substituents in styrene, and we should have obtained two Hammett plots with ρ values being the same or within striking distance for both the NaClO$_2$ and K$_3$[Fe(CN)$_6$] dihydroxylations. On the contrary, our reaction rate measurements afforded two Hammett plots with distinctively different ρ values for both electron-donating and electron-withdrawing substituents on styrene (Figure 1). The shape of the reported Hammett plot for the chincona alkaloid accelerated osmylation step is remarkably different from the shape of our Hammett plots.[8] Sharpless et al. have shown that even though the Hammett plot for ligand accelerated osmylation step is not linear, there is no clear minimum at X = H when the chincona alkaloid is the rate accelerating ligand.

Having settled the matter of the rate-determining step, we now have to find an explanation to why there are significantly larger reaction constants ρ in the Hammett plot the of NaClO$_2$ dihydroxylations (−2.76 for electron-donating and 0.53 for electron-withdrawing groups) than for the corresponding K$_3$[Fe(CN)$_6$] dihydroxylations (−1.82 for electron-donating and 0.22 for electron-withdrawing groups). The hydrolysis of the osmium mono(glycolates) in NaClO$_2$ dihydroxylations is much more sensitive to the effects of electronic perturbation than the hydrolysis of the corresponding osmium mono(glycolate) in K$_3$[Fe(CN)$_6$] dihydroxylations. The large differences in ρ values can be interpreted in terms of the rate-determining hydrolysis of the osmium mono(glycolate) in NaClO$_2$ dihydroxylations being in fact the hydrolysis of osmium(VIII) mono(glycolate) **2** and not the hydrolysis of osmium(VI) mono(glycolate) **1**.

SCHEME 1. Oxidation of Osmium(VI) Mono(glycolate) to Osmium(VIII) Mono(glycolate) by NaClO$_2$ (L = (DHQD)$_2$PHAL)



We think that after the initial formation of the cyclic osmium(VI) mono(glycolate), an exothermic oxidation of **1** to **2** takes place in our catalytic asymmetric NaClO$_2$ dihydroxylations (Scheme 1). Computational studies have shown that if there is a sufficiently strong oxidant present in the reaction mixture, the oxidation of osmium(VI) mono(glycolates) **1** to osmium(VIII) mono(glycolates) **2** is a highly exothermic process.[9] The chlorite ion oxidizes organic compounds such as formaldehyde by attacking as a nucleophile to the electrophilic carbonyl-center.[10] Erdik et al. have reported that in related atom transfer oxidations of osmium mono(glycolate) by *N*-oxides a Λ-shaped Hammett plot is obtained.[11] Probably one could reason that by using biphasic reaction conditions, sodium chlorite and osmium(VI) mono(glycolate) **1** are in different phases and therefore not able to react. However, studies of asymmetric catalytic epoxidations with chiral (salen)Mn(III) catalysts have shown that the epoxidation proceeds without difficulties, although the stoichiometric bleach (NaOCl) oxidant and the catalyst are in separate phases.[12]

Scheme 2 proposes the possible hydrolysis mechanisms of osmium(VI) mono(glycolate) in K$_3$[Fe(CN)$_6$] dihydroxylations and osmium(VIII) mono(glycolate) in NaClO$_2$ dihydroxylations of styrenes with electron-withdrawing substituents. In our pH = 11.5 carbonate buffered reaction conditions, the most obvious nucleophile is an aqueous hydroxide-ion. Mechanism proposals I and II are presented in stepwise hydrolysis mechanisms where the rate-determining step is the nucleophilic hydroxide-ion attack on an electron poor osmium-center yielding a negatively charged

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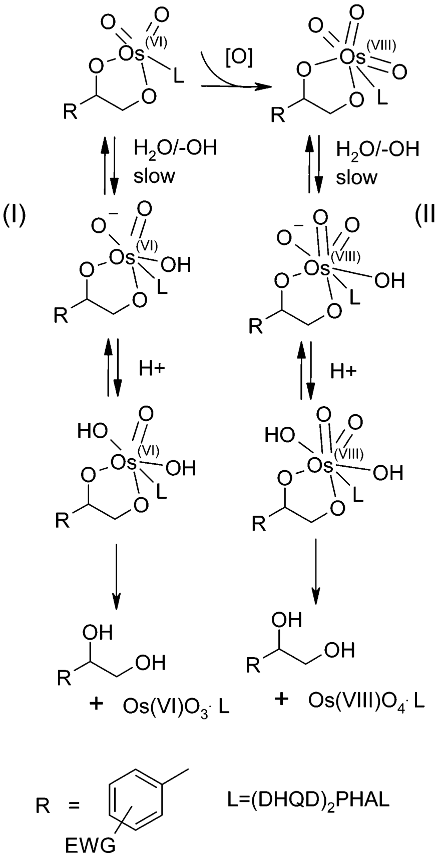
SCHEME 2. Mechanistic Presentation of the Hydrolysis Step in Catalytic Asymmetric $K_3[Fe(CN)_6]$ (I) and $NaClO_2$ Dihydroxylation (II) of Styrenes Containing Electron-Withdrawing Substituents



alkaline intermediate. The development of a negative charge in the transition state leading to an alkaline intermediate is consistent with a positive ρ value in the Hammett plots for the hydrolysis of osmium glycolates of styrenes with electron-withdrawing substituents (0.53 for $NaClO_2$ and 0.22 for $K_3[Fe(CN)_6]$ dihydroxylations). Even though the ρ values are small due to the low amount of negative charge developed during the slow step, some interpretation of the results can be made. Due to resonance stabilization, the alkaline intermediate in the hydrolysis of osmium(VIII) mono(glycolate) **2** is energetically more favorable than the corresponding alkaline intermediate in the hydrolysis of osmium(VI) mono(glycolate) **1**. Therefore, the rate-limiting nucleophilic attack on the electron poorer osmium(VIII)-center is faster in $NaClO_2$ dihydroxylations compared to the corresponding osmium(VI)-center in $K_3[Fe(CN)_6]$ dihydroxylations. Subsequent protonation of the alkaline intermediate and rearrangement of the intermediate product then releases the diol and the catalyst. The lack of the solvent kinetic isotope effect in both $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations of *p*-cyanostyrene indicates that a proton transfer is not involved in the rate-determining step in the hydrolysis of osmium glycolates with electron-withdrawing groups, and the hydrolysis is a stepwise process.

The inverse solvent kinetic isotope effect in the asymmetric dihydroxylation of *p*-methoxystyrene in $NaClO_2$ dihydroxylations indicates a specific acid catalysis mechanism in the hydrolysis step in the dihydroxylation of styrenes containing electron-donating substituents. The small k_{D2O}/k_{H2O} value (=1.35) suggests that although the proton transfer is incomplete, it is high enough to assume a certain amount of fast proton transfer to oxygen. Large negative ρ values in the Hammett plots (−2.76 for $NaClO_2$ and −1.82 for $K_3[Fe(CN)_6]$ dihydroxylations) for the dihydroxylation of styrenes with electron-donating substituents implicate that the hydrolysis mechanism involves a high degree of positive charge in the transition state. We suggest that hydrolysis of osmium(VIII) mono(glycolate) with electron-donating substituents in $NaClO_2$ dihydroxylations is an A1 process, as presented in Scheme 3. The slow step in the A1 process involves unimolecular cleavage of the protonated osmium(VIII) mono(glycolate) to yield a positively charged oxonium ion at the remaining ring-oxygen. In the hydrolysis of acetals a much larger k_{D2O}/k_{H2O} value (2.5−3.3) has been proposed to characterize an A1 mechanism.[13] The small k_{D2O}/k_{H2O} value combined with a high negative ρ value can be explained by a concerted proton attack on the osmium(VIII) mono(glycolate) followed by an assisted O−Os bond cleavage.

We were also interested to know if the reaction rates and nature of the substituted styrenes have an effect on the enantioselectivity in catalytic asymmetric dihydroxylations. Figures 2 and 3 present the enantioselectivities and pseudo-first-order rate constants of $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations of *p*-methoxystyrene, styrene, and *p*-cyanostyrene. Figures 2 and 3 show clearly that there is some correlation between the reaction rate and the enantioselectivity of the reaction. In both $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations, the slowest reacting olefin, styrene, afforded the poorest enantioselectivity. The 3-fold increase in the reaction rate improved the enantioselectivity of the $K_3[Fe(CN)_6]$ dihydroxylation of *p*-methoxystyrene by 1.5% compared to styrene, and a 1.5-fold increase in the reaction rate improved the enantioselectivity of *p*-cyanostyrene by 1.5%. In $NaClO_2$ dihydroxylations, the 6-fold increase in the reaction rate improved the enantioselectivity of the dihydroxylation of *p*-methoxystyrene by 3%, and a 2.5-fold increase in the reaction rate in $NaClO_2$ dihydroxylation of *p*-cyanostyrene improved the enantioselectivity by 2% compared to styrene.

Our results show that the nature of the substituted styrene cannot explain the variation in enantioselectivities in the asymmetric dihydroxylation of substituted styrenes in $K_3[Fe(CN)_6]$ dihydroxylations. We suggest that the so-called “secondary reaction cycle” that deteriorates enantioselectivity in NMO-oxidized asymmetric dihydroxylations operates also in $K_3[Fe(CN)_6]$ dihydroxylations. The activation barrier of the reaction yielding osmium(IV) bis(glycolate) from the corresponding mono(glycolate) in $K_3[Fe(CN)_6]$ dihydroxylations appears to be quite low. Frunzke et al. have calculated that the addition of a second ethylene molecule to the osmium(VI) ethyl mono(glycolate) yielding osmium(IV) ethyl bis(glycolate) is slightly endothermic (+0.8 kcal/mol).[9] In several reports the activation enthalpy for formation of osmium(VI) ethyl mono(glycolate) from $Os(VIII)O_4$ and ethylene varies from 0.8 to 5 kcal/mol.[14] Therefore, it seems that if the hydrolysis rate is slow enough, the osmium(VI) mono(glycolate) has access to the “secondary reaction cycle”, and the formation of bis(glycolate) becomes significant in terms of the overall enantioselectivity of the reaction.

Electronic effects have an effect on the rate at which the undesired bisglycolation occurs.[15] Electron-donating groups

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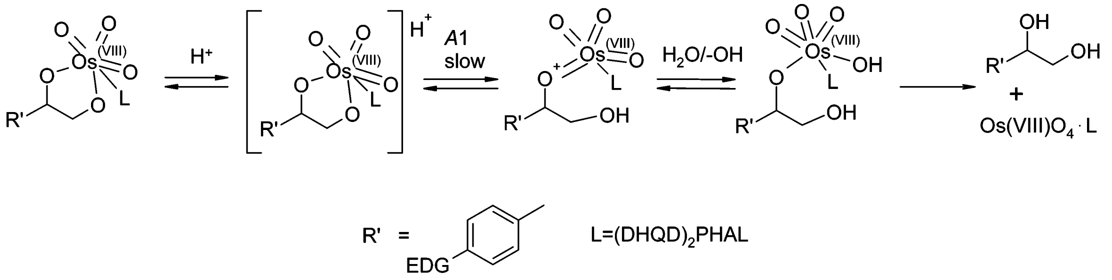
SCHEME 3. Mechanistic Presentation of the Hydrolysis Step in Catalytic Asymmetric $NaClO_2$ Dihydroxylation of Styrenes Containing Electron-Donating Substituents



accelerate and electron-withdrawing groups retard the rate at which the bisglycolation occurs. Therefore, the enantioselectivities of *p*-methoxystyrene and *p*-cyanostyrene are the same in $K_3[Fe(CN)_6]$ dihydroxylation, even though the reaction rate of *p*-methoxystyrene is twice the reaction rate of *p*-cyanostyrene. In the $NaClO_2$ dihydroxylation of *p*-methoxystyrene, the acceleration rate of the hydrolysis step is so high that it surpasses the deteriorating effect of the bisglycolation, even though the electron-donating methoxy-group increases the rate at which the bisglycolation occurs. Therefore, the enantioselectivities of the $NaClO_2$ and $K_3[Fe(CN)_6]$ dihydroxylations of *p*-methoxystyrene are the same.

In $NaClO_2$ dihydroxylations, enantioselectivities are 0−2% poorer than the enantioselectivities in $K_3[Fe(CN)_6]$ dihydroxylation, even though the reaction rates are 0- to 2-fold higher (Figures 2 and 3). The reaction rates of the dihydroxylation of styrene is almost the same in $NaClO_2$ dihydroxylations and $K_3[Fe(CN)_6]$ dihydroxylations, but the difference in enantioselectivity is the greatest. We believe that the oxidation of the intermediate osmium(VI) mono(glycolate) **1** to osmium(VIII) mono(glycolate) **2** prior to hydrolysis slightly diminishes the enantioselectivity in our $NaClO_2$ dihydroxylations. On the basis of enthalpy calculations on osmium(VI) ethyl mono(glycolate) and osmium(VIII) ethyl mono(glycolate) reported in the literature, we think that the bisglycolation of osmium(VIII) mono(glycolate) to osmium(VI) bis(glycolate) is a highly exothermic process compared to the slightly endothermic bisglycolation of osmium(VI) mono(glycolate) to osmium(IV) bis(glycolate).[9] Therefore, the hydrolysis rate of osmium(VIII) mono(glycolate) in the catalytic asymmetric $NaClO_2$ dihydroxylation is more significant in terms of the enantioselectivity than the hydrolysis rate of osmium(VI) mono(glycolate) in the asymmetric $K_3[Fe(CN)_6]$ dihydroxylation. The 3% difference in enantioselectivities between the fastest and slowest dihydroxylations in $NaClO_2$ dihydroxylations, compared to the 1.4% difference in $K_3[Fe(CN)_6]$ dihydroxylations, is a consequence of the different bisglycolation rates of the intermediate osmium(VI) mono(glycolates) and osmium(VIII) mono(glycolates).

In $NaClO_2$ dihydroxylations, the electronic features of the alkenes have more significant effects on the hydrolysis rates, and there is approximately a 2.5-fold increase in the reaction rate in the dihydroxylation of *p*-cyanostyrene and a 1.5-fold increase in the $K_3[Fe(CN)_6]$ dihydroxylation of *p*-cyanostyrene compared to the corresponding dihydroxylations of styrene. Simultaneously the cyano-group has a retarding effect on the rate by which the bisglycolation of the osmium(VIII) mono(glycolate) occurs which it also has on the bisglycolation of the osmium(VI) mono(glycolate). The opposite effects of the two competing reactions seem to improve the enantioselectivity of the asymmetric dihydroxylation of *p*-cyanostyrene by 2.2% in the $NaClO_2$ dihydroxylation and only 1.3% in the corresponding $K_3[Fe(CN)_6]$ dihydroxylation.

Conclusions

Our Hammett study and the results from the solvent kinetic isotope effect have led to a better understanding of the details in the hydrolysis step of catalytic asymmetric $K_3[Fe(CN)_6]$ and $NaClO_2$ dihydroxylations. A specific acid catalyzed A1 process and a stepwise hydroxy-ion attack on the electron-poor osmium-center and subsequent protonation of the alkaline intermediate operate in the rate-determining hydrolysis step in pseudo-first-order reaction conditions. The higher reaction rates in $NaClO_2$ dihydroxylations compared to $K_3[Fe(CN)_6]$ dihydroxylations are due to the oxidation of an osmium(VI) mono(glycolate) to the corresponding osmium(VIII) mono(glycolate) prior to hydrolysis, and thus the rate-limiting hydrolysis step is accelerated. Our results accompanied with computational studies show that the so-called "secondary reaction cycle" deteriorates the enantioselectivity in $NaClO_2$ dihydroxylations and also in $K_3[Fe(CN)_6]$ dihydroxylations but to a lesser extent.

Experimental Section

Kinetics. The kinetic studies were performed in a 50 mL three-necked flask equipped with a magnetic stirring bar, pH electrode, and thermometer. The flask was charged with 85 μmol of olefin, 1.5 mg (1.9 μmol, 2.2 mol %) of ligand $(DHQD)_2PHAL$, and 0.83 g (6.0 mmol) of K_2CO_3. The pH was adjusted to 11.5 with $NaHCO_3$. In the $NaClO_2$ dihydroxylations, 7.3 mg (1.5 equiv, 0.13 mmol) of $NaClO_2$ (80%), in addition to olefin, ligand, and base, was dissolved in 10 mL of a *t*-BuOH/H_2O (1:1) mixture. In the $K_3[Fe(CN)_6]$ dihydroxylations, 85 mg (3 equiv, 0.26 mmol) of $K_3[Fe(CN)_6]$, in addition to olefin, ligand, and base was dissolved in 10 mL of a *t*-BuOH/H_2O (1:1) mixture. The reactions were initiated by adding 76 μL (0.9 mol %) of a 10 mM $K_2OsO_4{\cdot}2H_2O$ solution to a cooled (0.5 °C) reaction mixture. The reactions were followed by monitoring the consumption of olefin. Aliquots of 20 μL were withdrawn from the reaction mixture after periods of time. The reaction was quenched by diluting the sample with a mixture containing 20 μL of a 60 mM solution of Na_2SO_3 and 20 μL of 0.017 mM acetophenone (standard) in EtOAc. The sample was dried with Na_2SO_4 prior to analysis with GC. The product isolation was performed on reactions with *p*-methoxystyrene, styrene, and *p*-cyanostyrene as the substrates. Na_2CO_3 (80 mg) was added, and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was transferred to a 50 mL separating funnel with 10 mL of EtOAc. The phases were separated, and the organic layer was washed with 5 mL of 1.2 M HCl, 5 mL of saturated Na_2CO_3, and 5 mL of brine. The organic layer was dried with Na_2SO_4 and filtrated, and the solvent was removed on a rotary evaporator. The products were analyzed without further purification.

1-(Methoxyphenyl)ethane-1,2-diol: ^{1}H NMR (200 MHz, acetone-*d*) δ 7.30 (d, J = 8.7, 2H), 6.87 (d, J = 8.7, 2H), 4.63 (m, 1H), 4.20 (d, $J = 3.3$, 1H), 3.72 (s, 3H), 3.74 (m, 1H), 3.54 (br, 2H); HRMS m/z (M + Na) found 191.0714, calcd 191.0684 ($C_9H_{12}O_3$-Na).

1-Phenylethane-1,2-diol: ^{1}H NMR (200 MHz, acetone-*d*) δ 7.25 (br, 5H), 4.72 (m, 1H), 4.30 (d, $J = 3.8$ Hz, 1H), 3.81 (m, 1H), 3.57 (br, 2H); HRMS m/z (M + Na) found 161.0575, calcd 161.0578 ($C_8H_{10}O_2Na$).

4-(1,2-Dihydroxyethyl)benzonitrile: ^{1}H NMR (200 MHz, acetone-*d*) δ 7.73 (d, $J = 8.1$, 2H) 7.62 (d, $J = 8.1$, 2H), 4.81 (m, 1H), 4.64 (d, $J = 3.8$ Hz, 1H), 3.96 (m, 1H), 3.62 (m, 2H); HRMS m/z (M + H) found 164.0684, calcd 164.0712 ($C_9H_{10}NO_2$).

The Solvent Kinetic Isotope Effect. A 50 mL three-necked flask equipped with a magnetic stirring bar, pH electrode, and thermometer was charged with 85 μmol of 4-methoxystyrene or 4-cyanostyrene, 1.5 mg (1.9 μmol, 2.2 mol %) of ligand $(DHQD)_2PHAL$, and 0.83 g (6.0 mmol) of K_2CO_3. The pH was adjusted to 11.5 with $NaHCO_3$. In the $NaClO_2$ dihydroxylations, 7.3 mg (1.5 equiv, 0.13 mmol) of $NaClO_2$ (80%), in addition to olefin, ligand, and base, was dissolved in 10 mL of a *t*-BuOH/D_2O (1:1) mixture. In the $K_3[Fe(CN)_6]$ dihydroxylations, 85 mg (3 equiv, 0.26 mmol) of $K_3[Fe(CN)_6]$, in addition to olefin, ligand, and base, was dissolved in 10 mL of a *t*-BuOH/D_2O (1:1) mixture. The reactions were initiated by adding 76 μL (0.9 mol %) of a 10 mM $K_2OsO_4 \cdot 2H_2O$ solution to a cooled (0.5 °C) reaction mixture. The reactions were followed by monitoring the consumption of olefin. Aliquots of 20 μL were withdrawn from the reaction mixture after periods of time. The reaction was quenched by diluting the sample with a mixture containing 20 μL of a 60 mM solution of Na_2SO_3 and 20 μL of 0.017 mM acetophenone (standard) in EtOAc. The sample was dried with Na_2SO_4 prior to analysis with GC.

Supporting Information Available: All experimental procedures, table, and plots of the kinetic data for all reported Hammett studies and kinetic solvent isotope effect studies, ^{1}H NMR spectra of the isolated products, and ^{1}H NMR spectra of the bis(Mosher's)-esters of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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